

Exhibit R



Do Clinical Data from Transgender Adolescents Support the Phenomenon of “Rapid Onset Gender Dysphoria”?

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Although emergence of gender dysphoria at puberty is long established, a distinct pathway of rapid onset gender dysphoria was recently hypothesized based on parental data. Using adolescent clinical data, we tested a series of associations that would be consistent with this pathway, however, our results did not support the rapid onset gender dysphoria hypothesis. (*J Pediatr* 2022;243:224-7).

Puberty has long been understood as one period when gender dysphoria often first emerges.¹ Although most transgender (trans) older adolescents and adults report needing gender-affirming medical care (hormones and/or surgeries), and also report having been aware of their gender at young ages,² only a small proportion receive gender-affirming care as adolescents. Use of hormonal suppression with a gonadotrophic-releasing hormone agonist, and hormones such as estrogen and testosterone therapies in trans and gender-diverse adolescents is supported by the American Academy of Pediatrics, the Pediatric Endocrine Society, the Endocrine Society, and the World Professional Association for Transgender Health.^{1,3-5} Referrals to adolescent gender clinics have increased internationally, particularly among those assigned female at birth.⁶⁻⁹

In 2018, a phenomenon of rapid onset gender dysphoria was hypothesized as a distinct pathway involving social contagion among youth vulnerable due to mental or neurodevelopmental disorders,¹⁰⁻¹² raising public concerns regarding potential for later regret following gender-affirming medical care. This discussion has occurred primarily in the context of data from a single online parental survey.^{10,11} Although this parental study has generated controversy,¹³ methodologic and social critique,^{12,14,15} and calls for additional research,^{16,17} its hypotheses have not yet been tested on data from youth themselves. Specifically, rapid onset gender dysphoria is hypothesized as a phenomenon in youth with gender dysphoria emerging at or after puberty, socially influenced through peer contagion, and with contributing factors including poor mental health, neurodevelopmental disabilities, parent-child conflict, and maladaptive coping strategies.^{10,11}

If the rapid onset gender dysphoria hypothesis indeed characterizes a distinct clinical phenomenon, and these youth access referrals for hormone suppression or gender-affirming hormones, then we would expect to see differentiation within clinical samples between those with more-recent (ie, rapid-onset) vs more-remote knowledge regarding their gender. Based on the published hypothesis,¹⁰ we would expect more recent gender knowledge to be associated with self-reported mental health measures, mental health and neurodevelopmental disability diagnoses, behaviors consistent with maladaptive coping (eg, self-harm), support from

online and/or transgender friends but not parents, and lesser gender dysphoria. We aim to test these hypotheses.

Methods

Baseline data (2017-2019) from the Trans Youth CAN! Cohort included pubertal/postpubertal adolescents age <16 years attending a first referral visit for hormone suppression or gender-affirming hormones at 10 Canadian medical clinics that provide specialized gender-affirming care to adolescents through a range of different care models. Ethics approval was received from all study sites. Years gender was known was missing for 1 participant (excluded), for a final sample of $n = 173$. Methods and measures are described in detail elsewhere.¹⁸

Self-reported measures were obtained from baseline interviewer-administered adolescent surveys,¹⁹ and diagnoses from baseline clinical records.²⁰ Recent gender knowledge was coded by subtracting age in years from age adolescents self-reported they “realized your gender was different from what other people called you.” As ages were whole numbers, a difference of 1 could indicate <1 year to just under 2 years. Values ≤ 1 were coded as recent gender knowledge, with an alternate definition (values ≤ 2) for sensitivity analysis. Mental health symptoms were assessed with the Overall Anxiety Severity and Impairment Scale,²¹ the Modified Depression Scale,²² and the Kessler-6 scale for psychological distress.²³ Mental health diagnoses extracted from chart included anxiety, depression, personality disorder, eating disorder, and neurodevelopmental disorder diagnoses

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*List of additional members of the Trans Youth CAN! Study Group is available at www.jpeds.com (Appendix).

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included autism, obsessive compulsive disorder, or attention deficit hyperactivity disorder. Gender dysphoria symptoms were assessed using the Trans Youth CAN! Gender Distress Scale.²⁴ Self-reported mental health behaviors included self-harm, substance use, and suicidal behavior. Three measures captured social connections to online and trans communities: having gender-supportive online friends was coded if adolescents reported online friends who knew their gender and were “very supportive,” and having online or trans friends as general sources of support was indicated in checklist items. Parental support was coded if youth indicated all biological/step/foster parents were “very supportive” of their gender identity or expression.

Statistical analyses were conducted using SAS v 9.4.1 (SAS Institute, Inc), weighted to account for clinics’ different recruitment periods due to staggered start dates, to improve generalizability.¹⁸ For analyses of associations between recency of gender knowledge and hypothesized correlates, a series of multiple regressions was conducted, with recency as the independent variable of interest, controlling for age and sex assigned at birth. Linear regressions were used for continuous dependent variables (eg, psychometric scales). For dichotomous dependent variables, modified Poisson regression with robust variance estimation was used.²⁵ As “rapid-onset” has not been precisely defined, we conducted a sensitivity analysis repeating these analyses using the alternate (value ≤ 2) definition of recent gender knowledge.

Results

Recency of gender knowledge is presented in the [Figure](#), results of hypothesized associations (recency value ≤ 1) in [Table I](#), and

variable means and frequencies in [Table II](#) (available at www.jpeds.com). Controlling for age and sex assigned at birth, recent gender knowledge was not significantly associated with depressive symptoms, psychological distress, past diagnoses with mental health issues or neurodevelopmental disorders, gender dysphoria symptoms, self-harm, past-year suicide attempt, having gender-supportive online friends, general support from online friends or transgender friends, or gender support from parents. Recent gender knowledge was associated with lower scores on anxiety severity/impairment ($b = -3.272$; 95% CI $-5.172, -1.373$), and lower prevalence of marijuana use (prevalence ratio = 0.11; 95% CI 0.02, 0.82), counter to hypothesized directions of effect. For sensitivity analysis using the alternate (value ≤ 2) definition of recent gender knowledge, we found all results substantively the same in statistical significance and direction of effect, except past-year marijuana use, which now only approached statistical significance ($P = .0677$).

Discussion

We did not find support within a clinical population for a new etiologic phenomenon of rapid onset gender dysphoria during adolescence. Among adolescents under age 16 years seen in specialized gender clinics, associations between more recent gender knowledge and factors hypothesized to be involved in rapid onset gender dysphoria were either not statistically significant, or were in the opposite direction to what would be hypothesized. This putative phenomenon was posited based on survey data from a convenience sample of parents recruited from websites,¹⁰ and may represent the perceptions or experiences of those parents, rather than of

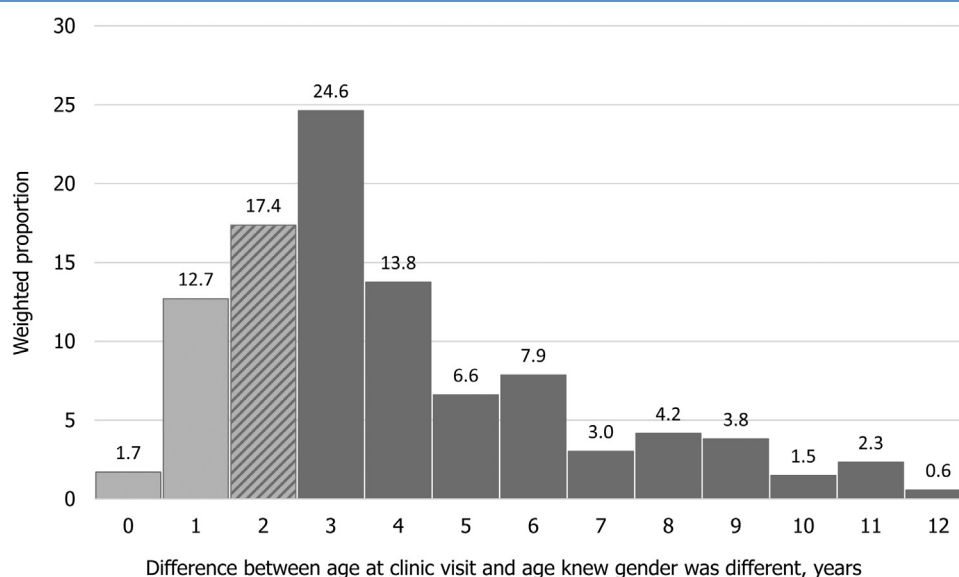


Figure. Recency of gender knowledge among adolescents age <16 years referred to Canadian clinics for hormone suppression or gender-affirming hormones ($n = 173$). Age at which knew gender was different was subtracted from current age in years; thus, “2 years” could range from more than 1 year to less than 3 years. Lighter gray represents recent gender knowledge in this analysis, with a sensitivity analysis also including the patterned bar.

Table I. Associations between short-term awareness of gender and variables hypothesized to be associated with rapid-onset gender dysphoria, controlling for age and sex assigned at birth

Dependent variables	B*	SE	P	PR*	95% CI†
Mental health scales					
Anxiety severity/impairment (OASIS)	−3.272	0.961	.0008		(−5.172, −1.373)
Depressive symptoms (MDS)	−1.276	0.845	.1328		(−2.944, 0.392)
Psychological distress (K6)	−1.156	1.060	.2771		(−3.248, 0.936)
Record of diagnosis with mental health disorder‡	−0.509	0.315	.1059	0.60	(0.32, 1.11)
Record of diagnosis with neurodevelopmental disorder§	0.066	0.362	.8563	1.07	(0.52, 2.17)
Gender dysphoria/distress (TYC-GDS)	−0.193	0.122	.1139		(−0.434, 0.047)
Mental health related behaviors					
Self-harm, past year	−0.052	0.191	.7833	0.95	(0.65, 1.38)
Marijuana use, past year	−2.178	1.010	.0310	0.11	(0.02, 0.82)
Past-year suicide attempt	−0.592	0.785	.4505	0.55	(0.12, 2.58)
Social connection indicators¶					
Reports having online friends supportive of gender	−0.050	0.157	.7505	0.95	(0.70, 1.29)
Indicates online friends as source of general support	−0.223	0.286	.4366	0.80	(0.46, 1.40)
Indicates trans friends as source of general support	−0.049	0.298	.1016	0.61	(0.34, 1.10)
All parents supportive of gender identity/expression	−0.004	0.202	.9836	1.00	(0.67, 1.48)

B, beta regression; K6, Kessler-6 Scale; MDS, Modified Depression Scale; OASIS, Overall Anxiety Severity and Impairment Scale; PR, prevalence ratio; TYC-GDS, Trans Youth CAN! Gender Distress Scale.

*Estimates adjusted for age in years and sex assigned at birth.

†95% CIs for betas (for linear regressions) or PRs (for modified Poisson regressions).

‡Extracted from medical record: any diagnosis from clinic or referrer of anxiety, depression, personality disorder, eating disorder. Personality disorder diagnoses were uncommon (n = 2) and no youth had a record of eating disorder diagnosis.

§Extracted from medical record: any diagnosis from clinic or referrer of attention deficit hyperactivity disorder, obsessive compulsive disorder, or autism.

¶Hypothesized by other authors based on a survey of parents recruited from websites generally unsupportive of gender-affirming care.¹⁰

adolescents, particularly those who may enter into clinical care. Similar analyses should be replicated using additional clinical and community data sources. Our finding of lower anxiety severity/impairment scores in adolescents with more recent gender knowledge suggests the potential for longstanding experiences of gender dysphoria (or their social complications) playing a role in development of anxiety, which could also be explored in future research. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

What Changed the Prognosis of Juvenile Dermatomyositis?

Sullivan DB, Cassidy JT, Petty RE, Burt A. Prognosis in childhood dermatomyositis. *J Pediatr* 1972;80:555-63.

The addition of systemic corticosteroids to the treatment of juvenile dermatomyositis played a pivotal role in changing the outcome of this disease. This commentary published 50 years ago summarized the demographic, clinical, laboratory, pathology, treatment, and outcome of 18 children with dermatomyositis seen between 1960 and 1969 in a single center. The medical treatment consisted of systemic corticosteroids with tapering over 2 years. In a previous classic report from 1964,¹ on which we wrote a commentary in 2014,² only 33% were treated with corticosteroids. The outcomes were grim: one-third died, another one-third remained crippled, and only one-third recovered completely. However, in this study merely 8 years later, no deaths from dermatomyositis were recorded. Seventeen of the 18 children were functionally independent after treatment, but 8 of 18 developed calcinosis. Four patients had residual skin scarring, 4 developed mild joint contractures, and 6 had muscle atrophy. It is important to note that most of the cases in this series (13/18) were mild and monophasic, and only 5 patients had dyspnea or dysphagia indicative of a more severe disease, thus contributing to the good prognosis.

Modern aggressive therapy includes corticosteroid-sparing medications. Methotrexate is given as first-line treatment together with corticosteroids. Other medications for severe or chronic disease include intravenous immunoglobulin, calcineurin inhibitors, cyclophosphamide, and biologic modifiers (rituximab and tumor necrosis factor inhibitors). Janus kinase inhibitors have shown promise. Overall, mortality has decreased to 2.5%. However, even today, between 30% and 40% of the patients manifest a chronic disease course with functional impairments and develop calcinosis, and they require long-term immunosuppressive therapy with many potential complications.³ Thus, despite the improvement in prognosis, there is still a long way to optimize treatment of this rare disease. Precision medicine, using specific myositis autoantibodies and analysis of immune pathways in individual patients, may further improve the outcome of our patients.³ In addition, early diagnosis and treatment are key!

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Appendix

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Table II. Weighted frequencies or means for sociodemographic and study variables (n = 173)

Variables	Value
Age, n (% _{weighted})	
10-11 y	17 (8.5)
12-13 y	37 (22.6)
14-15 y	119 (68.9)
Ethnoracial background,* n (% _{weighted})	
Indigenous	33 (18.4)
Nonindigenous visible minority [†]	10 (6.6)
Nonindigenous white	128 (75.0)
Immigration background, n (% _{weighted})	
1 or more immigrant parent	126 (28.7)
No immigrant parents	44 (71.3)
Living environment, n (% _{weighted})	
City	87 (55.2)
Suburb	59 (33.9)
Rural	27 (10.9)
Gender identity, n (% _{weighted})	
Male or primarily a boy	125 (75.7)
Female or primarily a girl	32 (15.9)
Nonbinary [‡]	14 (8.3)
Mental health scales, mean _{weighted} (SD)	
Anxiety severity/impairment (OASIS)	8.842 (4.548)
Depressive symptoms (MDS)	15.077 (4.030)
Psychological distress (K6)	10.746 (5.100)
Record of diagnosis with mental health disorder, [§] n (% _{weighted})	92 (51.6)
Record of diagnosis with neurodevelopmental disorder, [¶] n (% _{weighted})	44 (25.9)
Gender dysphoria/distress (TYC-GDS), mean _w (SD)	4.048 (0.557)
Mental health related behaviors, n (% _{weighted})	
Self-harm, past year	110 (67.9)
Marijuana use, past year	29 (20.0)
Past-year suicide attempt	24 (16.9)
Social connection indicators,** n (% _{weighted})	
Reports having online friends supportive of gender	109 (69.9)
Indicates online friends as source of general support	79 (49.3)
Indicates trans friends as source of general support	92 (55.8)
All parents supportive of gender identity/expression	109 (61.8)

K6, Kessler-6 Scale; MDS, Modified Depression Scale; OASIS, Overall Anxiety Severity and Impairment Scale; TYC-GDS, Trans Youth CAN! Gender Distress Scale.

*Coded to match Statistics Canada categories of Indigenous, visible minority, and white. Nonwhite, nonindigenous ethnoracial backgrounds were indicated by the following numbers of participants: 6 Black Canadian or African American, 2 Black African, 4 Latin American, 4 East Asian, 1 Indo-Caribbean, 3 Black Caribbean, 1 Middle Eastern, and 1 Southeast Asian (participants could indicate more than 1).

[†]The Canadian government defines visible minorities as "persons, other than Aboriginal peoples, who are non-Caucasian in race or nonwhite in color."²⁶

[‡]Response option was "nonbinary or something other than male or female."

[§]Extracted from medical record: any diagnosis from clinic or referrer of anxiety, depression, personality disorder, eating disorder. Personality disorder diagnoses were uncommon (n = 2) and no youth had a record of eating disorder diagnosis.

[¶]Extracted from medical record: any diagnosis from clinic or referrer of attention deficit hyperactivity disorder, obsessive compulsive disorder, or autism.

**Hypothesized by other authors based on a survey of parents.¹⁰